REMARKS

I. Status of the claims

Claims 70-72, 74-77, 79-83, 88, 92-94, 97-99, 116 and 130-133 have been amended, claims 1-69, 73, 78 and 129 have been canceled and claims 99-128 are withdrawn. Thus, claims 70-72, 74-77, 79-98 and 130-162 are currently under active examination. The amendments to claims 70 and 116 are to correct minor typographical errors. Claim 133 has been amended to improve clarity of the claim language. Furthermore, withdrawn claim 99 has been amended to further define that host cells are "provided nutrients by perfusion or through a fed-batch process." This amendment is meant to put language in agreement with language currently recited in independent claim 70. Amendments to claims 71-72, 74-77, 79-83, 88, 92-94, 97-98 and 130-132 are to correct claim dependencies. No new matter has been added. Applicants reserve the right to reintroduce canceled or amended claims in a future continuation application.

Because the subject matter of withdrawn claims 99-128 has been searched by the Examiner, Applicants request rejoinder of claims 99-128.

II. Examiner Interview

On Tuesday, June 24, 2008 a telephonic interview concerning this application was held between the Examiner and representative for the Applicants, Jeffery S. Sharp. During the interview the Examiner indicated that the claimed methods for adenoviral purification employing cell culture systems wherein nutrients are provided by perfusion or batch-fed methods should be free of the prior art. Thus, if claims were amended to overcome pending objections then the claims would likely be allowable. Furthermore, the Examiner indicated that if claim 99 and claims dependent thereon are amended to incorporate the claim feature concerning cell culture using a perfusion or batch-fed system then claim 99 and claims dependent thereon would also likely be allowable. Pursuant to suggestions made by the Examiner applicants have amended claims 71-72, 74-77, 79-83, 88, 92-94, 97-98 and 130-132 such that they now depend on claims 70 and have amended claim 99 to incorporate the perfusion or batch-fed feature regarding cell culture. Hence, all pending claims (claims

70-72, 74-77, 79-98 and 130-162) and previously withdrawn/now reintroduced claims (claims 99-128) are now believed to be allowable.

III. Priority claim

The Examiner asserted that dependent claims (*i.e.*, claims 79 and 140) concerning serum-free media usage are not adequately supported in the provisional application (U.S. Patent Application No. 60/031,329) to which the current case claims the benefit of priority. However, no separate rejection of claims 79 or 140 have been made and therefore Applicants need not take a position regarding this issue at this time.

IV. Claim objections and claim rejections under 35 U.S.C. §112 are now moot

The Examiner objected to claims 71, 72, 74-77, 79-98 and 130-132 because they depended from canceled claim 129. Furthermore, claims 71, 72, 74-77, 79-98 and 130-132 were rejected under 35 U.S.C. §112 as lacking proper antecedent bases for the term "claim 129." In response, Applicants have amended the indicated claims to depend from claim 70 and thus the objections and rejections are now believed moot.

V. The rejection under 35 U.S.C. § 103 should be withdrawn

The Examiner rejected claims 70 and 133-162 as obvious under 35 U.S.C. § 103, over Shabram *et al.* (U.S. Patent 5,837,520), Huyghe *et al.* (Human Gene Therapy, 1995), Kozak *et al.* (Developments in Biological Standardization, 1996), Keay *et al.* (Biotechnology and Bioengineering, 1976), Nadeau *et al.* (Biotechnology and Bioengineering, 1996) and Griffiths (Animal Cell Biotechnology, 1986). Applicants maintain that many of the cited references are not relevant to the rejection *made with respect to the main independent claim 70*, from which all the remaining claims depend. In any case, none of the cited references teach or suggest the use of perfusion or batch-fed cell culture systems in the production or purification of adenovirus. Furthermore, none of the cited references teach or suggest adenoviral purification methods that enable production of adenoviral compositions with the claim recited level of purity (*i.e.*, low level of nucleic acid contamination). Thus, Applicants maintain that no *prima facie* case for obviousness has been set forth.

The Examiner asserts that the skilled artisan would have been motivated to apply batch-fed culture systems to adenoviral purification methods by the teachings of Nadeau. In response, Applicants provided evidence, in the form of a declaration from Dr. Peter Clarke, that a person of ordinary skill in the art would recognize that the teachings of Nadeau concern methods for *recombinant protein production* and not methods for *production or purification of adenovirus*. Not only would the skilled artisan recognize that methods Nadeau do to not concern virus production, having reviewed Nadeau, the skilled worker would have reasonably concluded that cell culture methods disclosed in Nadeau would result in decreased virus yield. Finally, Nadeau assesses the effect of cell culture environment on protein production levels and does not concern the purity of resultant preparations. Thus, the skilled worker seeking an improved method for *purification* of adenovirus (*e.g.*, for therapeutic use) would neither be motivated to apply cell culture methods of Nadeau to virus production nor reasonably expect that such combination would result in enhanced purity of the preparation.

The declaration of Dr. Peter Clarke provides evidence that a skilled artisan would recognize the Nadeau *does not* provide any teaching relevant virus production. In particular, Dr. Clarke states that "[M]y review of Nadeau, other journal articles, and my own experience in the field of biotechnology form the basis of my conclusion that the person skilled in the art would not have considered the *protein production* methods of Nadeau to be equally applicable to *virus production* and certainly they would not have been considered applicable to methods of virus purification." (Clark declaration, paragraph 3) In Dr. Clarke's detailed analysis of Nadeau he notes that "Nadeau never quantified viral production in their system," rather all studies were directed to analysis of *protein production*. (Clark declaration, paragraph 5) Furthermore, Dr. Clarke states that the skilled artisan would recognize that protein production described in Nadeau *would not* correlate with virus particle production. Thus, a skilled artisan would not have been able to derive any information from Nadeau regarding what kind of cell culture conditions would enhance virus yield and thus be useful for virus *production* much less virus *purification*.

Furthermore, even if the skilled artisan attempted to draw a conclusion from the studies of Nadeau with regard to virus particle production, the skilled artisan would have concluded that cell culture methods of Nadeau would likely result in *low virus yield*. The

declaration of Dr. Clark highlights that the studies of Nadeau clearly show ongoing metabolic activity in cells used in protein production. Such ongoing metabolic activity is inconsistent with high-level virus production which causes cytopathic effect and cellular metabolic shutdown (*see, e.g.*, paragraph 6 of the Clarke declaration). Thus, a skilled worker would have concluded that methods of Nadeau were incompatible with virus production and therefore Nadeau teaches away from the claimed method of virus purification.

Finally, the skilled artisan would have been unable to predict *a priori* that use of batch-fed (or perfusion) cell culture systems in virus purification would have any effect on the purity of resultant virus preparations, much less result in preparations with enhanced purity as disclosed in the present application. It was not until Applicants applied these new culture systems to adenoviral purification that such an enhancement in purity became apparent. Thus, the result of the combination of cell culture methods of Nadeau with adenoviral purification would have had no predictable outcome and therefore the combination would not have been obvious at the time the instant application was filed. In view of the foregoing, applicants assert that no *prima facie* case for obviousness has been set forth.

VI. Conclusion

Applicants believe that pending claims 70-72, 74-77, 79-98 and 130-162 and previously withdrawn claims 99-128 are now in condition for allowance and such favorable action is requested. The Examiner is invited to contact Jeffery Sharp or the undersigned at 312-474-6300 to discuss the case.

Dated: July 3, 2008

Respectfully submitted,

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